HFA-305
(Dockets Management Branch)

JAN 11 2000

FREEDOM OF INFORMATION SUMMARY
Oxyglobin® Solution
NADA # 141-067

Sponsor: BIOPURE Corporation
11 Hurley Street
Cambridge, MA 02141

FOIS 1

Table of Contents

FREEDOM OF INFORMATION SUMMARY

1. GENERAL INFORMATION:

NADA Number: 141-067

Sponsor: Biopure Corporation
11 Hurley Street
Cambridge MA 02141

Generic Name: Hemoglobin glutamer-200 (bovine)

Trade Name: Oxyglobin® Solution

Marketing Status: Rx: Federal (USA) law restricts this drug to use by or on the order of a licensed veterinarian.

Effect of the supplement: This supplement changes the original approval from a fixed dosage of 30 mL/kg to a flexible dosage range of 10-30 mL/kg.

2. INDICATIONS FOR USE:

Oxyglobin® is indicated for the treatment of anemia in dogs by increasing systemic oxygen content (plasma hemoglobin concentration) and improving the clinical signs associated with anemia, regardless of the cause of anemia (hemolysis, blood loss, or ineffective erythropoiesis).

3. DOSAGE FORM, ROUTE OF ADMINISTRATION, AND RECOMMENDED DOSAGE:

Oxyglobin® is a sterile, clear, dark purple solution containing 13 g/dL purified, polymerized hemoglobin of bovine origin in a modified Lactated Ringer's Solution.

DOSAGE FORM: Injectable

ROUTE OF ADMINISTRATION: Intravenous at a rate of up to 10 mL/kg/hr

DOSAGE AND ADMINISTRATION:

The recommended dosage of Oxyglobin® is a one-time dose of 10-30 mL/kg of body weight administered intravenously at a rate of up to 10 mL/kg/hr. The choice of dose within the recommended range will vary with the patient and the clinical situation.

Pharmacokinetic data show that there is an increase in the duration of action with increasing dose.

4. EFFECTIVENESS:

The effectiveness of Oxyglobin® at the lower dose was established by the following studies:

LABORATORY TISSUE OXYGENATION STUDY

A) Title:	Correction of tissue hypoxia associated with acute normovolemic anemia: A comparison of polymerized bovine-derived hemoglobin and erythrocytes in a canine model
B) Principal Investigator:	Thomas G. Standl, MD Eppendorf University Hospital Martinistrasse 52 20246 Hamburg, Germany
C) Design of Study:	
1) Purpose of Study:	To examine skeletal muscle tissue oxygen tension after severe acute normovolemic anemia, comparing the effects of cumulative equivalent doses of hemoglobin in the form of stored red cells, freshly donated blood and polymerized bovine hemoglobin in a canine model.
2) Test Animals:	24 Foxhounds divided into 3 groups of 8 dogs each.
3) Groups:	Group 1:Banked red blood cells (stored for 3 weeks) Group 2: Fresh blood Group 3: HBOC-201 (HBOC- hemoglobin based oxygen carrier)
4) Methods:	Acute normovolemic hemodilution model: for each dog, blood was withdrawn and simultaneously replaced with 6% hetastarch to target hematocrit values of 20%, 15% and 10% while maintaining pulmonary capillary wedge pressure.
5) Dosage Form:	Injectable

Biopure has developed two different HBOC formulations, HBOC-201, and HBOC-301, Oxyglobin®. The two solutions are similar with the exception of the absolute molecular weight distribution. They are both based on an ultra-purified, glutaraldehyde polymerized, bovine hemoglobin in a modified Lactated Ringers buffer. The processing steps are similar with the exception of a final filtration step for HBOC-201 to remove low molecular weight hemoglobin. There are no differences in the oxygen binding and release characteristics of the two products as shown by nearly identical equilibrium curves for HBOC-201 and Oxyglobin®.

6) Route of Administration: Intravenous

7) Dosage Used: 3 stepwise infusions of hemoglobin to achieve a cumulative augmentation of 1, 2 and 3 g/dL total plasma hemoglobin

8) Test Duration: Group 1 dogs were phlebotomized (15 mL/kg) 3 weeks prior to treatment and the RBCs were stored. All dogs were hemodiluted immediately prior to treatment. The study was terminated on Day 1.

9) Pertinent Parameters: Skeletal muscle oxygen tension immediately following dosing.

D) Results:

In the dogs receiving HBOC-201, the mean baseline tissue oxygenation was restored by a hemoglobin augmentation of 0.7g/dL.

E) Conclusions:

The study results indicate that an increase in total hemoglobin by as little as 0.7 g/dL with HBOC-201 in plasma was associated with restoration of baseline tissue oxygen tension after severe hypoxia due to hemodilution.

PHARMACOKINETICS STUDY

A) Title: Noncompartmental pharmacokinetic analysis of plasma hemoglobin data from Study 2022-97

B) Principal Investigator:
Nancy Kelly, DVM DABT
ITR Laboratories
19601 Clark Graham
Baie d' Urfe, Quebec
Canada H9X 3T1

C) Design of Study:

1) Purpose of Study: To determine the pharmacokinetics of Oxyglobin® following a single intravenous infusion in a model of acute isovolemic hemodilution.

2) Test Animals: 18 Beagle dogs divided into 3 groups of 6 dogs each.

3) Control: None

4) Diagnosis: Acute isovolemic hemodilution model: blood was withdrawn and simultaneously replaced with Lactated Ringer's Solution to a target hematocrit of 15% while maintaining central venous pressure.

5) Dosage Form: Injectable.
The formulation HBOC-301, Oxyglobin®, was used in this study.

6) Route of Administration: Intravenous

7) Dosage Used: 7, 10, 15 mL/kg

8) Test Duration: Dogs were hemodiluted immediately prior to infusion. Blood was collected within 1 minute after the completion of the infusion and at 1, 3, 6, 12, 18, 24 and 30 hours post infusion and twice daily until Day 7.

9) Pertinent Parameters: Total plasma hemoglobin concentration

D) Results:

The following table contains a summary of the pharmacokinetic parameters:

Dose mL/kg	Duration (hours)*: oxyglobin levels over 1 g/dL	Terminal half-life (hours)*
7	4 - 9	17-25
10	11 - 23	18-26
15	23 - 39	19-30

*range based on mean ±SD

E) Conclusions:

In this study, an Oxyglobin® (hemoglobin based oxygen carrier) dose of 10 mL/kg provides a 1 g/dL plasma hemoglobin level for 11 to 23 hours.

CONCLUSIONS REGARDING EFFECTIVENESS

1. The laboratory tissue oxygenation study shows that augmentation of plasma hemoglobin concentration by as little as 0.7 g/dL with a hemoglobin based oxygen carrier in plasma restores tissue oxygenation to baseline levels.

2. The pharmacokinetics study shows that an Oxyglobin® (hemoglobin based oxygen carrier) dose of 10 mL/kg can provide 1 g/dL plasma hemoglobin.

3. Together, these studies support the effectiveness of 10 mL/kg of Oxyglobin® as the lower end of the dosage range.

5. SAFETY:

The safety of Oxyglobin® is based on data in the original approval (refer to the Freedom of Information Summary dated January 12, 1998.) This supplement provides a lower dose range than in the original approval.

6. HUMAN SAFETY:

Human Safety Relative to Food Consumption: Data on human safety, pertaining to consumption of drug residues in food, were not required. This drug is to be labeled for use in dogs which are non-food animals.

Human Safety Relative to Possession, Handling, and Administration: labeling contains an adequate caution statement.

7. AGENCY CONCLUSIONS:

The data in support of this supplemental NADA comply with the requirements of Section 512 of the Act and Section 514.111 of the implementing regulations, and demonstrate that Oxyglobin® (hemoglobin glutamer-200 (bovine)) when used under labeled conditions of use, is safe and effective.

Under section 512(c)(2)(F)(iii) of the FFDCA, this approval for non food producing animals qualifies for THREE years of marketing exclusivity beginning on the date of approval because the application contains substantial evidence of the effectiveness of the drug involved, or studies of animal safety required for the approval of the application conducted or sponsored by the applicant.

The drug is restricted to use by or on the order of a licensed veterinarian because professional expertise and proper diagnosis are required to: 1) determine the need for oxygen carrying support, 2) use a drug intended for intravenous infusion which requires close monitoring and possible adjustment of infusion rate, and 3) recognize and treat, if necessary, adverse reactions to the drug.

The following patents claim Oxyglobin®: 5,084,558 (exp. 1/28/09), 5,296,465 (exp. 3/22/11) and 5,618,919 (exp. 4/8/14).

8. LABELING (attached)

a. Package insert (draft)

Labels for the bag overwrap, carton, and shipper were not changed by this supplemnetal approval.

Oxyglobin® Solution

hemoglobin glutamer - 200 (bovine)

FOR INTRAVENOUS USE IN DOGS ONLY

CAUTION: Federal (USA) law restricts this drug to use by or on the order of a licensed veterinarian.

DESCRIPTION: Oxyglobin® contains 13 g/dL polymerized hemoglobin of bovine origin in a modified Lactated Ringer's Solution containing Water for Injection USP 100 g/dL, NaCl USP 113 mmol/L, KCl USP 4 mmol/L, $CaCl\text{-}2H_2O$ USP 1.4 mmol/L, NaOH NF 10 mmol/L, Sodium Lactate USP 27 mmol/L, N-acetyl-L-cysteine USP 200 mg/dL. It has an osmolality of 300 mOsm/kg. It is a sterile, clear dark purple solution with a pH of 7.8. It is a distribution of hemoglobin polymers with less than 5% of the hemoglobin as unstabilized tetramers, approximately 50% has a molecular weight between 65 and 130 kD, and no more than 10% has a molecular weight >500 kD. It contains less than the detectable level of 3.5 µg/mL free-glutaraldehyde and 0.05 EU/mL endotoxin.

PHARMACOLOGY: Oxyglobin® is a hemoglobin-based oxygen carrying fluid which increases plasma and total hemoglobin concentration and thus increases arterial oxygen content. The terminal elimination half-life of the drug is estimated to range between 18 and 43 hours for dosages of 10-30 mL/kg (Table A) in dogs. The increase in half-life with dose suggests a saturable elimination process. Depending on the dose, greater than 95% of the administered dose is expected to be eliminated from the body at 4 to 9 days after infusion. A laboratory study in dogs established that an increase in total hemoglobin by as little as 0.7 mg/dL with a hemoglobin-based oxygen carrying fluid restored normal tissue oxygenation.[1] Table A provides data from a laboratory study on the post-infusion duration (hours) for which plasma Oxyglobin® levels remained above this therapeutically critical level (1 g/dL).

Table A Pharmacokinetic parameters at multiple dose levels after a single infusion of Oxyglobin®

Dose (mL/kg)	Immediate post infusion concentration (g/dL)	Duration (hours): Oxyglobin® levels over 1 g/dL	Terminal half-Life* (hours)	Cleared from plasma (days)***
10	1.5 – 2.0	11 – 23	18 – 26	4 – 5
15	2.0 – 2.5	23 - 39	19 – 30	4 – 6
21	3.4 – 4.3	66 - 70	25 – 34	5 – 7
30	3.6 – 4.8	74 - 82	22 – 43**	5 – 9**

* range based on mean ± SD
**range based on estimated mean value with bounds of a 95% prediction interval
***range based on 5 terminal half-lives

Metabolism and Excretion: In a toxicokinetic study involving 24 healthy young adult male Beagle dogs, transient hemoglobinuria was noted for less than 4 hours after completion of the Oxyglobin® infusion. The duration of hemoglobinuria in diseased dogs has not been determined.

INDICATIONS: Oxyglobin® is indicated for the treatment of anemia in dogs by increasing systemic oxygen content (plasma hemoglobin concentration) and improving the clinical signs associated with anemia, regardless of the cause of anemia (hemolysis, blood loss, or ineffective erythropoiesis) (See EFFECTIVENESS).

CONTRAINDICATIONS: Plasma volume expanders, such as Oxyglobin®, are contraindicated in dogs with a pre-disposition to volume overload such as those with advanced cardiac disease (i.e., congestive heart failure) or otherwise severely impaired cardiac function or oliguria or anuria. The safety of Oxyglobin® was not assessed in dogs with these conditions.

WARNINGS: Overdosage or an excessively rapid administration rate (i.e., > 10 mL/kg/hr) may result in circulatory overload.

OVERDOSAGE: Accidental overdosage or an excessive rate of administration (i.e., >10 mL/kg/hr) could result in immediate cardiopulmonary effects, in which case infusion of Oxyglobin® should be discontinued immediately until signs abate. Signs of circulatory overload such as pulmonary edema, pleural effusion, increased central venous pressure, dyspnea, or coughing may occur. Treatment of circulatory overload may be necessary.

[1] Bovine Haemoglobin is More Potent than Autologous Red Blood Cells in Restoring Muscular Tissue Oxygenation after Profound Isovolaemic Haemodilution in dogs. Standl T., et al. *Can J Anaesth.* 43(7):714-723.

PRECAUTIONS: The safety and efficacy of repeat administration of Oxyglobin® have not been demonstrated in dogs. The safety of Oxyglobin® for use in breeding dogs and pregnant or lactating bitches has not been determined. Teratogenic effects were observed in preliminary reproductive toxicity studies in rats using a related polymerized bovine hemoglobin product. The safety and efficacy of Oxyglobin® have not been evaluated in dogs with disseminated intravascular coagulopathy, thrombocytopenia with active bleeding, hemoglobinemia and hemoglobinuria, or autoagglutination.

If an immediate hypersensitivity reaction occurs, infusion of Oxyglobin® should be immediately discontinued and appropriate treatment administered. If a delayed type of hypersensitivity reaction occurs, immunosuppressant therapy is recommended.

Concomitant treatment of the cause of anemia should be instituted.

Treatment with Oxyglobin® at a dosage of 30 mL/kg results in a mild decrease in PCV immediately post infusion. Due to the dilutional effects of Oxyglobin® at that dose, PCV and RBC count are not accurate measures of the degree of anemia for 24 hours following administration. Dilutional effects are not seen at a dosage of 15 mL/kg.

The animal should be adequately hydrated (but not overhydrated) prior to administration. Due to the plasma expanding properties of Oxyglobin®, the possibility of circulatory overload should be considered especially when administering adjunctive intravenous fluids, particularly colloidal solutions. If concurrent fluid therapy is administered, it should be temporarily discontinued during infusion of Oxyglobin®. Close monitoring of central venous pressure (CVP) during and immediately following administration of Oxyglobin® is recommended. If CVP measurement is not feasible, the patient should be carefully monitored for signs of circulatory overload. If CVP increases to a clinically unacceptable level and/or if signs of circulatory overload are observed, the infusion of Oxyglobin® should be temporarily discontinued and reinstituted at a slower rate when signs abate and/or CVP decreases. Use of a diuretic may be indicated.

Clinical Pathology:

Chemistry: The presence of Oxyglobin® in serum may result in artifactual increases or decreases in the results of serum chemistry tests, depending on the type of analyzer and reagents used.

Table B: Valid Analytes by Instrumentation

Idexx VetLab	Hitachi All Models	Johnson & Johnson Ektachem/Vitros	Dupont Dimension	Beckman CX7/CX3
sodium	sodium	sodium	sodium	sodium
potassium	potassium	potassium	potassium	potassium
chloride	chloride	chloride	chloride	chloride
BUN	BUN	BUN	BUN	BUN
CK	CK	CK	LDH	calcium
creatinine	glucose	AST	calcium	glucose
	ALT	calcium		
	AST	magnesium		
	calcium	lipase		
		glucose		

Hematology: No interference. Confirm that hemoglobin is measured, not calculated from red blood cell number.

Coagulation: Prothrombin time (PT) and activated partial thromboplastin time (aPTT) can be accurately determined using methods that are mechanical, magnetic, and light scattering. Optical methods are not reliable for coagulation assays in the presence of Oxyglobin®. Fibrin degradation products can be measured using the Thrombo-Wellcotest kit (Murex® Kent, England).

Urinalysis: Sediment examination is accurate. Dipstick measurements (i.e., pH, glucose, ketones, protein) are inaccurate while gross discoloration of the urine is present.

SAFETY: The safety of Oxyglobin® was assessed in 40 healthy Beagle dogs with induced acute, severe normovolemic anemia (total hemoglobin concentration ≈ 5 g/dL). Oxyglobin® was administered at 0, 30, 60, and 90 mL/kg twice at a 72 hour interval (equivalent to 0, 1X, 2X, 3X the maximum recommended dose given twice, respectively). 13% Human Serum Albumin (HSA) in Saline was a control (90 mL/kg twice at 72 hour interval) used to determine the effects of a protein load compared with Oxyglobin®. There was 100% survival in all groups.

The clinical and pathological effects associated with Oxyglobin® were: ***Transient clinical signs:*** yellow-orange discoloration of the skin, ear canals, pinnae, mucous membranes (gums), and sclera, red-dark-green discoloration of feces, brown-black discoloration of urine, red spotting of skin and/or lips (less common finding) and decreased appetite and thirst. Vomiting, diarrhea, and decreased skin elasticity occurred within 48 hours of dosing. The frequency and/or intensity of these clinical signs were dose dependent. ***Clinical pathology:*** transient, dose

dependent red discoloration of plasma, increases in serum enzyme activity with no corresponding microscopic lesions in the liver: 8-fold mean increase in aspartate aminotransferase (AST) activity (peak activity 200 and 677 U/L at 1X and 2X doses given twice, respectively) and 5-fold mean increase in alanine aminotransferase (ALT) activity at 3X dose given twice only (peak activity 372 U/L), increase in serum total protein (peak concentration 9.9 and 14.6 g/dL at 1X and 3X doses given twice, respectively), and hemoglobinuria.

Gross pathology: Dark yellow-orange-brown discoloration (whole body) and dark areas on gall bladder serosa. ***Histopathology:*** Hemosiderin in the renal cortex, arteriolitis (limited duration) and activation of tissue macrophages in multiple organs occurred in all Oxyglobin® treated groups. Microscopic hemorrhage in the gall bladder and evidence of hepatic macrophage activation occurred in only the 2X and 3X dose groups given twice. Reversible, slight to mild renal tubular damage with limited distribution was seen in both the Oxyglobin® treated and HSA in Saline treated control dogs. All findings were dose dependent except for renal tubular protein droplets and casts (indicating saturation of tubular protein reabsorption) and a slight proliferative glomerulopathy (limited duration and distribution) seen in all Oxyglobin® treated groups.

Immunohistopathology: Immunofluorescent antibody staining was performed on kidneys of Oxyglobin® treated dogs in which a glomerulopathy was identified (5/24) to detect deposition of immune complexes. Only one dog with a glomerulopathy (graded slight) had a focal non-specific IgG deposit in a single area in the outer cortex of one kidney in an estimated amount of 30%. Deposits of <25% is considered normal in dogs.

Immunology: Low levels of canine immunoglobin-G class antibodies to bovine hemoglobin (anti-BvHb) were produced in 11/12 Oxyglobin® treated dogs. Due to the limited nature of the study, no relationship between anti-BvHb antibody titer and dose of Oxyglobin® administered could be demonstrated. Observed levels of IgG anti-BvHb are not expected to have any toxicological significance in dogs.

ADVERSE REACTIONS: The clinical field trial included dogs with anemia (PCV 6-23%) due to hemolysis (immune mediated, naphthalene toxicity), blood loss (gastrointestinal, traumatic, surgical, rodenticide intoxication), and ineffective erythropoiesis (idiopathic, red cell aplasia, ehrlichiosis, chronic renal failure). Adverse reactions were tabulated by frequency in treated dogs (n=52). The following adverse reactions may be related to Oxyglobin® and/or the underlying disease.

Table C: Frequency of Adverse Reactions in Oxyglobin® Treated Dogs

Adverse Reaction	% of Treated Dogs with Adverse Reaction (n=52)
Discoloration	
Mucous Membranes°	69
Sclera (yellow, red, brown)	56
Urine (orange, red, brown)	52
Skin (yellow)	12
Cardiovascular	
Increased CVP†	33
Ventricular Arrhythmia✓	15
Ecchymoses/ Petechiae	8
Bradycardia	6
Gastrointestinal	
Vomiting	35
Diarrhea	15
Anorexia	8
Respiratory	
Tachypnea	15
Dyspnea	14
Pulmonary Edema	12
Harsh Lung Sounds/Crackles	8
Pleural Effusion	6
Miscellaneous	
Fever	17
Death/ Euthanasia	15
Peripheral Edema	8
Hemoglobinuria*	6
Dehydration	6

° yellow, red, purple, brown
† measured in 17 dogs only
✓ AV block, tachycardia, ventricular premature contractions
*measured in 3 dogs only

Adverse reactions occurring in 4% of the dogs treated with Oxyglobin® included: coughing, disseminated intravascular coagulopathy, melena, nasal discharge/crusts (red), peritoneal effusion, respiratory arrest, and weight loss (5-7% body weight). Adverse reactions occurring in less than 2% of the dogs treated with Oxyglobin® included: abdominal discomfort on palpation, acidosis, cardiac arrest, cardiovascular volume overload (by echocardiography), collapse, cystitis, dark stool, discolored soft stool (red-brown) and tongue (purple), focal hyperemic areas on gums, forelimb cellulitis/lameness, hematemesis or hemoptysis (unable to differentiate), hypernatremia, hypotension, hypoxemia, lack of neurologic responses, left forebrain signs, nystagmus, pancreatitis, pendulous abdomen, polyuria, pulmonary thromboembolism, ptosis, reddened pinnae with papules/head shaking, reduction in heart rate, thrombocytopenia (worsening), and venous thrombosis.

EFFECTIVENESS:
Dose Response Study: A controlled laboratory study was conducted in 30 healthy dogs with induced acute, severe normovolemic anemia (total hemoglobin concentration ≈ 3 g/dL). Oxyglobin®, administered once at a dose of 30 mL/kg, resulted in significantly ($p \leq 0.01$) increased arterial oxygen content at 60 minutes and 24 hours following dosing compared with control dogs. A positive correlation was established between arterial oxygen content (laboratory measured) and plasma hemoglobin concentration (clinically measured).

Clinical Field Study: A well controlled clinical field trial involving 64 client-owned dogs (2 months to 15 years old) weighing 2.1 to 71.8 kg with moderate-severe anemia (total hemoglobin concentration 1.7-6.9 g/dL and PCV 6-23%) was conducted at six clinical sites. Dogs were either treated with Oxyglobin® (30 mL/kg) or untreated (with an option to receive Oxyglobin® if condition worsened). Relative to pretreatment, plasma hemoglobin concentration significantly increased ($p \leq 0.001$) and clinical signs associated with anemia (lethargy/depression, exercise intolerance, and increased heart rate) significantly improved ($p \leq 0.001$) in the Oxyglobin® treated group for at least 24 hours. Treatment success, defined as the lack of need for additional oxygen carrying support (i.e., a blood transfusion) for 24 hours, was 95% in the Oxyglobin® treated group compared with 32% in the control group.

The effectiveness of the lower end of the dose range is supported by controlled laboratory studies (See PHARMACOLOGY).

DOSAGE AND ADMINISTRATION: The recommended dosage of Oxyglobin® is a **one time** dose of 10 – 30 mL/kg body weight administered intravenously at a rate of up to 10 mL/kg/hr (See PRECAUTIONS). The choice of dose within the recommended range will vary with the patient and the clinical situation. Pharmacokinetic data show that there is an increase in the duration of action with increasing dose. (See PHARMACOLOGY).

For recommendations on patient monitoring during and immediately following Oxyglobin® administration and discussion of conditions which may warrant adjustment in the administration rate see Precautions section. If desired, Oxyglobin® may be warmed to 37° C prior to administration.

Remove overwrap prior to use and use within 24 hours. Oxyglobin® should be administered using aseptic technique via a standard intravenous infusion set and catheter through a central or peripheral vein at a rate of 10 mL/kg/hr. Do not administer with other fluids or drugs via the same infusion set. Do not add medications or other solutions to the bag. Do not combine the contents of more than one bag.

Use of Oxyglobin® does not require cross-matching with recipient blood. A blood transfusion is not contraindicated in dogs which receive Oxyglobin® nor is Oxyglobin® contraindicated in dogs which have previously received a blood transfusion. Oxyglobin® is intended for single dose use. Any unused Oxyglobin® should be disposed of in accordance with local requirements for handling veterinary medical waste.

STORAGE CONDITIONS: *Store at room temperature or refrigerated (2-30° C).* DO NOT FREEZE. *Oxyglobin® remains stable for up to 24 months; the expiry date is printed on the bag.*

HOW SUPPLIED: Oxyglobin® is available as follows:

NDC 63075-301-01
125 mL single dose bags

NOT FOR HUMAN USE

Oxyglobin® Solution
Biopure Corporation
11 Hurley Street
Cambridge, MA 02141

NADA # 141-067, Approved by FDA
Revision December 99

Biopure Part Number 49-0060